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THE SHWARTZMAN PHENOMENON: A REVIEW WITH A CONSIDERATION OF SOME POSSIBLE DERMATOLOGICAL MANIFESTATIONS.

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THE Shwartzman phenomenon, a phenomenon of altered tissue reactivity, is a reaction of considerable general biological interest. It is possibly also the mechanism that produces certain dermatological manifestations the genesis of which has not so far been adequately explained. Since the American and English dermatological literature seems to have unduly neglected the Shwartzman phenomenon, a review would now appear to be timely.

The phenomenon was first described in the late nineteen hundred and twenties by Gregory Shwartzman, now of Mount Sinai Hospital in New York (1936, 1937). In this discussion it is probably best first to indicate how it is produced and then to consider its other properties. This review is concerned only with the major reasonably well-documented aspects of the phenomenon, and will not go into technical modifications and minutiae.

TABLE I.

<i>Route of injection.</i>	<i>Preparation.</i>	<i>Material injected.</i>
a. Into skin	}	Bacterial products.
b. Into vascular system of an organ		
c. Into general circulation		
<i>Incubation Period.</i>		
12-24 hours.		
<i>Elicitation.</i>		
Intravenous injection	{	Bacterial products.
		Antigens to which host is sensitive.

The rabbit is the usual experimental animal ; other species can be used, but the reaction is much more readily obtained in the rabbit. Table I shows that the process is essentially a two-stage one : the first is to prepare the tissue in which it is wished to develop the reaction ; the second is the eliciting or provocative injection. The preparatory filtrate can be put either into the skin, or into the vascular system of an organ, or into the general circulation. When it is put into the general circulation, and the reaction subsequently elicited by repeating the intravenous injection within the requisite time, a generalized and often fatal reaction occurs. This is usually known as the Sanarelli-Shwartzman phenomenon.* For the preparatory injection bacterial products are used—either micro-organisms or filtrates derived from them ; in most experimental procedures the latter have been used. The filtrates are usually derived from *Escherichia coli*, *Neisseria intracellularis*, and a polysaccharide obtained from *Serratia marcescens*. After the preparatory injection an interval must elapse before giving the eliciting injection ; that is there must be an incubation period. Twenty-four hours is usually allowed, probably more for convenience than for any other reason. It can be reduced to twelve hours and possibly less. No matter what route was used for the preparatory injection, the eliciting material must be given intravenously. The possible ramifications and widespread importance of the phenomenon can be appreciated by a consideration of the diversity of eliciting materials that may be used : the same bacterial product may be used again, *but* bacterial products totally unrelated in any usual taxonomic or immunological sense will also work. In fact, substances such as kaolin or agar, which ordinarily would be thought of as immunologically inert, can be used and one of the most important classes of substance that will elicit a reaction in a prepared site is an antigen-antibody complex or the products released by such a union. For example, if a rabbit has been sensitized to egg albumin and a Shwartzman filtrate is then injected into the skin, nothing happens. If now, 24 hours after the intracutaneous injection of the Shwartzman filtrate, the rabbit is given, by any route, the antigen to which it is sensitive, in this case egg albumin, a haemorrhagic necrotic reaction appears at the skin site. In normal non-sensitized rabbits such a sequence of injections does not produce lesions. The clinical significance of this will be considered later.

The hallmark of the Shwartzman reaction is microscopic haemorrhage followed by necrosis. Some hours, usually about four, after the eliciting injection, a haemorrhagic necrotic reaction appears at the site of the preparatory injection where at the time of the preparatory injection a grossly visible, mild inflammatory response may be noted but none need be present. No correlation

* The generalized reaction is usually referred to by the double eponym as Sanarelli, according to Urbach and Goldburgh (1942), first studied the generalized phenomenon. See also Sanarelli (1936).

can be made between the intensity of the inflammatory response that develops from the preparatory injection and the intensity of the reactions seen after the eliciting one. As Gerber (1936) states " . . . there is no parallelism between the skin-preparatory potency of a filtrate and the inflammation resulting from its intradermal injection." In the generalized phenomenon one sees diffuse haemorrhages in various viscera, but the pathognomonic feature is bilateral renal cortical necrosis (Thomas and Good, 1952). The only natural situation in which the generalized reaction can be produced by one injection is in the pregnant rabbit: the interest of this is that bilateral renal cortical necrosis in the human occurs, for all practical purposes, only during pregnancy.

The Shwartzman phenomenon and the Arthus reaction are often confused with each other both theoretically and clinically. The Arthus phenomenon, antedating the Shwartzman by many years, was described in the early years of this century by Maurice Arthus, a student of Richet, the discoverer of anaphylaxis. Table II briefly recapitulates the salient points of each.

TABLE II.

	<i>Shwartzman.</i>	<i>Arthus.</i>
Technique of preparation . . .	1 injection	1 or more injections.
Technique of elicitation . . .	Intravenous	Into tissue in which wish to develop.
Nature of preparatory substances	Micro-organisms or their products	Proteins; complex polysaccharides.
Nature of eliciting substances	A wide variety	The same as used for the preparation.
Incubation period :		
Preparation	24 hours	9 days.
Elicitation	4 hours	4 hours.
Specificity	None	High.
Relation to antibody	"	Requires precipitating antibodies.
Transferability	Not transferable	Transferable.
Persistence of reactive state	48-120 hours.	Months-years.
Relation to anaphylaxis . .	None	A form of
Pathology	Capillary thrombosis	Capillary thrombosis
	Capillary rupture	Capillary rupture.
	Haemorrhage into tissues	Haemorrhage into tissues.
	Necrosis	Necrosis.

It seems quite clear that the Shwartzman and Arthus phenomena are essentially different though there are points of similarity in their mechanisms, some of which will be discussed later. What is the nature of the Shwartzman phenomenon? Originally various workers (not Shwartzman) suggested that the process was a modified form of allergy. The author believes that much confusion about allergic concepts has arisen through lack of a precise definition of the term "allergy." In the light of present knowledge the following is suggested: *Allergy is an acquired specific alteration in the capacity to react brought about by an antibody mechanism.* Such a definition is precise and gives to

allergic processes a biological common factor, namely, the antibody mechanism. It should be noted that this definition requires some revision of the conventional concepts of what constitutes an antibody (Rostenberg and Brunner, 1950). This definition of allergy immediately excludes the Shwartzman phenomenon, for the phenomenon probably represents the summation of the effects of two irritants. The preparatory dose makes the tissue more vulnerable to certain subsequent effects which are brought about by the second intravenous injection. Until recently the nature of these changes was quite mysterious, but the work of Good and Thomas (1952), Stetson and Good (1951), Stetson (1951*a* and *b*) Thomas and Stetson (1949), Thomas and Good (1952*a* and *b*) has given a much clearer insight into the sequence of events that leads to the final haemorrhagic-necrotic Shwartzman reaction. According to the above workers, the sequence is somewhat as follows :

1. The preparatory injection causes an increase of aerobic glycolysis and an increased formation of lactic acid.

2. The preparatory injection causes granulocytes to accumulate in the injected area so as to form cuffs or sheaths about the smaller veins.

3. These alterations presumably make the tissue more vulnerable to the action of proteolytic enzymes, but it is kept from succumbing to them by the existence of the normal enzyme inhibitors.

4. The eliciting intravenous injection possibly nullifies the protease inhibitors so that the proteolytic enzymes can act on the vulnerable tissue to cause haemorrhage and necrosis.

5. The intravenous injection also causes the circulating platelets and polymorphonuclear leucocytes to clump into aggregates which are removed from the circulation by sequestration in the capillary bed of the lungs and other organs. A temporary leukopenia occurs in the peripheral blood as a consequence of the intravenous injection, regardless of whether the animal has a prepared site or not.

6. The granulocytic aggregates produced by the intravenous injection of the eliciting factor appear to be essential for the development of the haemorrhagic necrotic reaction; for, if by some preliminary treatment the granulocytes are so reduced that when the intravenous injection is given aggregates cannot be formed, the haemorrhagic necrotic reaction does not develop. For example, if nitrogen mustard be given between the preparatory and the eliciting doses the haemorrhagic reaction does not appear; but if the granulocytopenia ordinarily induced by nitrogen mustard be prevented, treatment with this material does not then inhibit the Shwartzman reaction.

7. It is believed that a prepared site is very vulnerable to interruption of the blood supply by such aggregates; death and disintegration of vessels, haemorrhage into the tissue and necrosis complete the picture.

Cortisone has some peculiar effects on the phenomenon; indeed, adequate

treatment of the rabbit with cortisone seems to serve as a substitute for the preparatory injection (Thomas and Good, 1952).

While the Arthus and the Schwartzman phenomena differ essentially in that the former is based on an antigen-antibody reaction, both end in haemorrhage and necrosis. The mechanism for the production of the final pathological changes is the same. Table III, taken from Stetson (1951), illustrates this.

TABLE III.—*Identical Mechanisms for the Production of the Pathological Alterations in the Schwartzman and the Arthus Phenomena.*

- a. Perivascular accumulation of polymorphonuclear leucocytes in injected skin areas.
- b. Increased aerobic glycolysis in injected skin areas.
- c. Leucocyte-platelet clumping *in vitro* by the eliciting agent.
- d. Leucopenia after injection of the eliciting agent.
- e. Leucocyte-platelet thrombosis of capillaries and small veins in injected area.
- f. Consequent haemorrhage from vessels involved in cellular thrombosis.

It is probably because an Arthus phenomenon induces the above changes that an antigen-antibody union is capable of causing the haemorrhagic necrotic reaction in a site prepared with a Schwartzman filtrate.

Table IV lists some of the conditions in which there is reason to believe a Schwartzman mechanism occurs (Black-Schaffer, 1949; Schwartzman *et al.*, 1936; Schwartzman, 1937; Schwartzman and Gerber, 1948). Before discussing them it should be pointed out that, even though it can be shown how the Schwartzman phenomenon could produce the entity in question, this is no proof that the lesions or the disease are actually produced by such a means, and there is no *a priori* reason why all or certain of the listed manifestations should not be produced in more than one way. While therefore a Schwartzman mechanism might be the correct explanation for a given case, it in no way follows that it is the correct or the only explanation for all cases of that same condition. Nevertheless it is felt that the Schwartzman reaction is the most logical pathogenetic explanation for the enumerated conditions that has so far been advanced. Apart from the intellectual satisfaction of understanding the means by which any clinical entity is produced, a better theoretical understanding often leads the way to practical clinical management.

In the discussion that follows no detailed consideration of the entities listed in Table IV is attempted. The purpose of this review is merely to list those conditions for which a Schwartzman mechanism has been suggested, and to suggest others for which such a pathogenesis seems not unlikely.

There is evidence that the first two internal conditions, bilateral renal cortical necrosis and the Waterhouse-Friderichsen syndrome, arise on the basis of a Schwartzman mechanism. They can be experimentally produced by such

a means. The Waterhouse-Friderichsen syndrome occurs with a meningococcaemia, and it is well known that the meningococcus is a potent Schwartzman filtrate producer.

Ulcerative colitis is a disease about which there has been much aetiological speculation. It is not the purpose here to go into the various theories except to state that various workers have suggested that a reasonable basis for the production of the lesions is a Schwartzman mechanism (Black-Schaffer, 1949; Schwartzman and Gerber, 1948; Winkelstein and Schwartzman, 1942; Winkelstein, 1946). The sequence of events postulated is somewhat as follows: in the intestinal wall an infection develops which serves as the Schwartzman preparatory factor, then circulating toxins from the same or an unrelated infection act as the eliciting factor. As evidence for this hypothesis, Ecker and Welch (1930) have developed lesions in the gastric mucosa of the rabbit by

TABLE IV.—*Clinical Conditions which possibly Develop by a Schwartzman Mechanism.*

Internal conditions :
Bilateral renal cortical necrosis.
Waterhouse-Friderichsen syndrome.
Ulcerative colitis.
Cutaneous conditions :
Purpuras :
Toxic—infectious.
Fulminans—gangrenosa.
Pyoderma gangrenosum.
Dermatitis gangrenosa infantum.
Dermatitis nodularis necrotica.
Lazarine leprosy.
Butcher's pemphigus.
Necrotic reactions to various antigens.
Heteroallergic manifestations.

injecting the preparatory dose there and subsequently injecting the eliciting dose intravenously. Latteri (1934) by similar methods has produced lesions in the appendix. One reason for emphasizing the possible Schwartzman aetiology of ulcerative colitis is the high frequency of its association with pyoderma gangrenosum, a condition which, I believe, develops on the same basis.

Turning now to the dermatological conditions, probably the most common of these to arise through such a mechanism are the infectious or toxic purpuras. The sequence of events is somewhat as follows: infective emboli lodge in the skin, thus constituting a preparatory site—parenthetically, it may be stated that in a meningococcaemia bacteria are often readily demonstrable in the skin (Schwartzman and Gerber, 1948). As a consequence of the infection from which the patient is suffering there are circulating toxins or toxic products, and these can serve as the eliciting factor. The purpuric haemorrhagic varieties of the various exanthemata may develop in a similar fashion, but it would be well

to point out that there are several possible mechanisms. Fisher and Kraszewski (1952), in discussing purpura following measles, state: "Purpura may be present during the course of the acute infectious fevers in three forms. First, it may be confined to the rash, where it is probably an exaggeration of the mechanism causing the exanthem. Secondly, it may occur in the haemorrhagic type of these infections, when it appears early and is associated with a severe illness which may prove fatal. This is probably due to septicaemia, often streptococcal, rather than to toxæmia from the primary infection. Thirdly, purpura may occur during the period of convalescence from scarlet fever (Box, 1933), rubella (Ackroyd, 1949) and measles (Miller, 1941)." While the Shwartzman phenomenon is not explicitly named by them, it should be clear that the second mechanism they consider is ideally suited for producing Shwartzman type reactions.

Several cases of purpura fulminans or gangrenous purpura have recently been reported in which a Shwartzman reaction has been mentioned as a pathogenetic possibility. (Lewi, 1948; Dunn, 1951; Chambers, Holyoke and Wilson, 1952).

It may be asked why a secondary infection is necessary—do not the conditions for the development of a Shwartzman reaction exist with any infection? The answer is that in part they do, as was pointed out above in connection with meningococcaemia, but a secondary infection often provides more favorable conditions for the reaction to develop, for reasons that may be mentioned briefly. First, two infections seem at times to have a synergizing effect, so that the damage produced is more severe than either alone will cause. The experiment of Gratia and Linz (1932) illustrates this nicely: They rubbed vaccinia virus into the skin of a rabbit, and 48 hours later, before any eruption occurred, injected an active bacterial filtrate intravenously. This transformed mild erythematous lesions into severe haemorrhagic necrotic ones. Koplik (1935) did similar experiments with the same results. Hog cholera caused by a virus may run a benign course until secondary bacterial infection provokes a necrotizing pneumonia and in some animals bilateral cortical renal necrosis (Röhrer, 1932).

Secondly, even though conditions with a given infection are propitious to develop a Shwartzman reaction, in that cutaneous preparatory foci exist and that there are circulating toxins, no reaction may ensue. The reason for this is that the host has developed antibodies against the circulating toxins which effectively neutralize them so that they cannot act as eliciting factors. If, however, a new infection supervenes, with the elaboration of new circulating toxic materials against which the body has not had opportunity to develop defences, these toxins can be the eliciting factor for the sites prepared by the first infection. On the other hand, the secondary infection may provide the skin preparatory sites; the original infection may not have been of such a

type as to furnish cutaneous foci, but may serve as an abundant source of circulating toxins ready to act on properly prepared areas when these become available.

Many observers have described severe haemorrhagic and gangrenous ulcerations of the skin associated with various septic processes, the most common of which is chronic non-specific ulcerative colitis. Brunsting, Goeckerman and O'Leary (1930) gave the name pyoderma (ecthyma) gangrenosum to such ulcers. This term has become popular, and most of the similar cases have have been reported under this title. Unfortunately, however, this diagnosis has no exact morphological or pathological criteria, and there is no agreement as to the pathogenesis of the ulcerations. Brunsting *et al.* pointed out that similar cases had been described earlier under a variety of labels. More recently Greenbaum (1941) writing on this subject believes the proper generic term for such cases is that used by Brocq, namely, Phagedena geometrica. He believes that the same condition has been variously described as pyoderma gangrenosum, chronic serpiginous ulcerative (and erosive) pyoderma, chronic pyoderma, chronic undermining burrowing ulcer, phagedenic ulceration, gangrenous ecthyma or impetigo, postoperative progressive serpiginous ulceration or gangrene in a clinical sense.

TABLE V.—*Synopsis of Cases of Pyoderma Gangrenosum.*

Authors and reference.	Title under which reported.	No. of cases reported.	Associated conditions.
Brunsting <i>et al.</i> (1930)	Pyoderma (ecthyma) gangrenosum	5	4 chronic ulcerative colitis. 1 empyema following influenza.
Comments by authors: A striking parallel relationship was demonstrated between the activity of the cutaneous lesions and the major infectious focus, the intestine. We believe that the cutaneous manifestations which are here described as pyoderma gangrenosum are but one part of a generalized infectious syndrome characterized by marked lowering of bodily resistance to the invading organisms. Healing of the cutaneous lesions is dependent on the successful treatment of systemic disease.			
McCarthy and Fields (1931)	Pyoderma gangrenosum	1	ulcerative colitis.
Comments by authors: Believe that the pyoderma gangrenosum is only a part of a generalized infection that results in marked lowering of body resistance which in itself permits invasion of the skin by the causative organisms.			
Lane, C. W., and Stroud, C. M. (1933)	Pyoderma gangrenosum	1	cholecystitis and pyuria.
Comments by authors: Was evident that the lesions of the skin were directly dependent on these conditions. Accompanying an exacerbation of either condition there was a marked recrudescence of the ulcers.			
Cohen, M. (1936)	Pyoderma (ecthyma) gangrenosum (A deficiency disease complex)	1	ulcerative colitis.
Comments by author: "... it is my opinion that this condition is not of an infectious nature but is due to the lack of some protective substance or vitamin in the skin and intestinal tract."			

TABLE V (continued).

Authors and reference.	Title under which reported.	No. of cases reported.	Associated conditions.
Weiss, H. B., Grollman, A. I., and Cohen, S. (1937)	Pyoderma gangrenosum .	1 .	infectious arthritis, upper respiratory infection, pleuritis and pericarditis.
Comments by authors : Goldman in the discussion suggested that the lesions might represent a Schwartzman reaction.			
Gibson, R. (1937)	Pyoderma gangrenosum .	1 .	?
Comments by author : No gross lesion was discovered which could give rise to a chronic infection in the body.			
Mintzer, I. J. (1939)	Pyoderma gangrenosum . onychogryphosis and onycholysis	1 .	ulcerative colitis.
Montgomery, D. W. (1939)	Pyoderma (ecthyma) gangrenosum	1 .	none.
Comments by author : At one time during the course of the disease the patient had a sharp attack of diarrhoea.			
Jankelson and McClure (1940)	Skin lesions during course of ulcerative colitis	7 .	ulcerative colitis.
Comments by authors : All occurred during height of an exacerbation. No specific organisms found, only staphylococci and streptococci.			
Weiner, A. L. (1940)	Pyoderma gangrenosum .	1 .	ulcerative colitis.
Greenbaum, S. S. (1941)	Phagedena geometrica . (Brocq)	6 .	1 ulcerative colitis, 1 lues (?), 2 trauma, 2 none determined.
Comments by author : See text of present article.			
Dostrovsky, A., and Sagher, F. (1943)	Phagedenic ulcer (pyoderma gangrenosum)	54 .	miscellaneous—often trauma.
Comments by authors : Use the term " phagedenic ulcer " to designate a peculiar type of chronic ulceration of the skin which tends to spread peripherally and is characterized by the presence of certain micro-organisms. The picture as described is apparently identical with the condition referred to by Brunsting <i>et al.</i> as pyoderma gangrenosum.			
Dostrovsky, A., and Sagher, F. (1946)	Ulcus phagedenicum cutis	58 .	miscellaneous—often trauma.
Comments by authors : Draw attention to the similarity of this disease to pyoderma gangrenosum or Meleney's ulcer.			
Kiel, V. L. (1947)	Pyoderma gangrenosum .	1 .	ulcerative colitis, arthritis and abscessed teeth.
Comments by author : Believes improvement followed extraction of abscessed teeth.			
Ricketts, <i>et al.</i> (1948)	Pyoderma (ecthyma) gangrenosum	3 .	ulcerative colitis.
Comments by authors : Correlate skin lesions with colitis and mention that in one case lesion healed after colon was resected.			
Russell, B. (1950)	Phagedenic and gan- grenous ulceration of the skin complicating ulcerative colitis (pha- gedena geometricum)	4 .	ulcerative colitis.
Comments by author : It is probable that the primary skin lesions arise from a generalized malnutrition with wide avitaminosis and hypo-proteinaemia. It is suggested that the phagedenic type of ulceration is precipitated by a critical degree of dehydration and is a manifestation of the depression of tissue reaction to infection produced thereby.			

Table V briefly summarizes certain information from the articles on pyoderma gangrenosum and allied conditions consulted in the preparation of this

paper. It is evident that under the label of pyoderma gangrenosum severe cutaneous ulcerations, apparently arising for a variety of reasons, have been reported. When the diagnostic caption has been phagedena geometricum an even wider variety of morphological pictures, surely aetiologically unrelated, have been included.

Various pathogenetic hypotheses for the ulceration have been put forward and can be grouped into three main categories: (i) it is a symbiotic infection; (ii) it is an infection owing its morphe and therapeutic intransigence to the nature of the soil; (iii) it is not an infection at all—or at least the prime determining factors are malnutrition and subsequent metabolic deviations. None of these theories has any experimental substantiation or even theoretical vindication. One difficulty in attempting to explain the genesis of the lesions is that the entire group constitutes an aetiological potpourri. To correct this a more careful screening of the cases and a more rigid classification are advisable.

It seems that these various haemorrhagic-phagedenic-gangrenous ulcerations can be divided into two main groups—those which are associated with some definite underlying septic focus and those which are not. In the latter, two distinct aetiological mechanisms are possible: (a) those produced by symbiotic infection, and (b) those in which a single organism is responsible but may require an impoverished or malnourished soil. In those with a definite underlying septic focus (it usually seems to be a chronic non-specific ulcerative colitis, but is not necessarily so) it is suggested that the mechanism producing the ulceration is the Shwartzman reaction. It is urged that the name pyoderma gangrenosum be reserved for this group, as it is believed desirable to have a designation for this aetiological-morphological complex, assuming it to be one. This label has the virtue of having been applied to the majority of such reported cases, so that it already has clinical acceptance. If it is desired to retain the term phagedena geometricum, it should be employed in a purely morphological sense to comprise all ulcerations of certain clinical characteristics (see Greenbaum, 1941), but the term should also imply that the case has not been sufficiently clarified for its aetiological basis to be determined.

The condition usually labelled dermatitis gangraenosa infantum is rare with a rather characteristic morphological appearance (Blatt *et al.*, 1938; Radcliffe-Crocker, 1888; Laurance *et al.*, 1952; Pasachof and Sobel, 1932; Walker and Low, 1910; Watson, 1934). It should be realized that while the lesions of the cases reported under this title share a common morphology and probably develop by the same pathogenic mechanism, they develop in association with a varied group of infections, most frequently the exanthemata, particularly vaccinia or varicella. In other words, the condition is a syndrome, not a disease *sui generis*, and it can complicate many infections. As a result, the lesions have been described under many names, such as pemphigus gangraenosa vaccinia gangraenosa, and varicella gangraenosa; there is a tendency in recent

years to report the condition under the name of the disease that it complicates. I prefer this, for to give it a name such as that coined by Radcliffe-Crocker (*Dermatitis gangraenosa infantum*) has nosological implications which are not warranted. The lesions were well described by Radcliffe-Crocker (1888), and his comments regarding the diagnosis still apply: "This is not difficult; with or without a history of varicella, the occurrence of numerous gangrenous ulcers in a young child, or even of deep ulcerations, beginning as a pustule, enlarging, drying into a scab in the centre, and then ulcerating, form a group of symptoms quite unmistakable." That obviously describes quite well the lesions of *pyoderma gangrenosum*, not surprisingly, as they probably develop by the same mechanism, namely, a Shwartzman reaction. Indeed, such a mechanism in *dermatitis gangraenosa infantum* was suggested as long ago as 1932 by Pasachoff and Sobel.

Dermatitis nodularis necrotica is a rare disease first described by Werther (1910). There have been relatively few cases reported, so that it would be hazardous for anyone, on the basis of the rather sparse existing knowledge, to be dogmatic about it (Duenling, 1930, 1936; Eichenlaub, 1930; Nieman and Wise, 1939). The morphological and clinical aspects of the disease appear to be fairly constant; a rather protracted illness with a more or less low-grade septic course and the development of many cutaneous lesions which are often haemorrhagic and necrotic.* Several cases have ended fatally, but it is difficult to be certain that death was really due to the disease. While the clinical picture is reasonably uniform, the views about the aetiology and pathogenesis seem to be somewhat divergent. In general there appear to be two subdivisions of this morphological entity. The first and larger one consists of cases with active tuberculosis elsewhere in the body, and the skin lesions are regarded as a form of papulo-necrotic tuberculide. In the second and smaller group, tuberculosis seems to have been definitely excluded, but there does appear to have been present some septic process which has never been clearly defined. The appearance and the intensity of the skin lesions seem to coincide reasonably well with the flaring of the underlying septic state.

From the pathological features, the clinical course, and the presence of an associated septic condition, it is reasonable to suggest that the cutaneous lesions in this second, smaller group of cases arise on the basis of a Shwartzman phenomenon. The mechanism would be similar to that already suggested, namely, the development of a skin infection or the localization of toxins in the skin and then the same or other toxins circulating from an internal focus, causing the haemorrhagic necrotic reaction. In the report by Nieman and Wise the patient at autopsy was found to have a bilateral necrotizing bronchopneumonia, which, according to various workers in the field, is a Shwartzman manifestation.

* A good colour plate of a moulage is included in the original article by Werther.

It is also possible that those cases of the larger group in which tuberculosis exists also develop the skin lesions by a Shwartzman phenomenon. The tuberculosis could supply a circulating toxin or act as the source of an antigen to which the patient is admittedly sensitive, so that the antigen-antibody union would be the factor eliciting the haemorrhagic necrotic reaction in a site prepared by the same or another infection. These remarks also apply to other forms of necrotic tuberculosis, such as papulo-necrotic tuberculides or erythema induratum. It may be that in these conditions there is an embolic distribution of tubercle bacilli, but it does not follow that the reaction is necessarily occasioned by the localization of the tubercle bacillus in the area. Indeed there is much evidence to show that this organism does not necessarily produce reactions by its mere presence. It would, however, be a reasonable explanation that the micro-organism, having become localized and having acted as a preparatory factor, renders the tissue vulnerable to the action of circulating toxins.

Lazarine leprosy is a rare form in which the predominating lesions are bullous and necrotic (Pardo-Castello and Caballero, 1931; Pardo-Castello and Piñeyro, 1948); its position in the classification of leprosy has always been a puzzling one. Pardo-Castello and Piñeyro believe that the lazarine type is not entitled to a separate category, but they regard it as a special clinical manifestation which can supervene in either the lepromatous or tuberculoid variety. From the description of the lesions, their pathology and the nature of leprosy, the mechanism of the reaction would apparently be best explained on a Shwartzman basis, an hypothesis that has been entertained by others. Pardo-Castello and Piñeyro quote Latapi and Chavez Zamora as believing that "... the type of bullous leprosy developed in lepromatous patients (Lucio's type) is the result of the Shwartzman phenomenon spontaneously produced in these patients as a result of a synergic sensitization to *M. leprae* and to different "cocci" present in foci of infection or as secondary invaders."

Butcher's pemphigus, pemphigus acutus febrilis gravis, is not a true pemphigus, i.e. it is not a form or phase of pemphigus vulgaris. Most authorities today regard it as a manifestation of an overwhelming septicaemia. Various German authors (Proppe, 1948; Richter, 1950) have suggested that the cutaneous lesions are a manifestation of the Shwartzman phenomenon. If the disease really has a septicaemic basis, such an interpretation would be quite reasonable and the mechanism in line with what has been suggested several times in this paper. Pfleger and Tappeiner (1951) go even further and speculate on the necrotic ulcerations seen in a case of pemphigus vegetans being brought about by the same mechanism.

Richter and John (1950) report a case of a generalised herpes zoster complicating Hodgkin's disease with fatal outcome. They interpreted the haemorrhagic lesions seen at autopsy as examples of a Sanarelli-Shwartzman phenomenon.

Clinically one of the most favourable opportunities for the development of a Shwartzman reaction is when the host encounters a substance to which he is sensitive at a time when he has an infection. This is possibly a much greater hazard than is currently appreciated. As has already been said, the giving of an antigen to which an animal is sensitive will cause a haemorrhagic necrotic reaction to appear on a prepared cutaneous site. Various authors have pointed out that such situations and such reactions are not very uncommon in clinical medicine. Harkavy and Romanoff (1939) go into this possibility quite fully and cite several illustrative cases. A prototype of these cases is the following: A patient is being injected with a bacterial vaccine and has received repeated intradermal or subcutaneous injections without any untoward effect. It so happens that this person is sensitive to ragweed. During the ragweed season the vaccine injections are continued, when suddenly one of the sites becomes haemorrhagic and sloughs out.

The suggested explanation is that the intradermal vaccine injections act as preparatory sites, but nothing happens as there is no eliciting factor until the ragweed season when the patient inhales the antigen to which he is sensitive. An antigen-antibody union takes place, with the subsequent breakdown of the prepared site. Obviously there can be many variations on this general theme.

Urbach and Goldburgh (1942) described a severe bullous haemorrhagic and necrotic reaction after an intradermal test with 0.000002 mg. of tuberculin P.P.D. They interpreted the reaction as being brought about by a Shwartzman mechanism. The patient died 26 days after the last tuberculin injection. At autopsy haemorrhagic changes were found suggesting a generalised Sanarelli-Shwartzman phenomenon, and the authors speculate on the possible relation of this to the local reaction. The French, especially Gougerot and his collaborators, have reported several somewhat analogous cases.

Lewi (1949), under the general title of "the secondary syndrome of chemotherapy," which he has shortened to the term "sanergie," attempts to explain many of the accidents seen as a consequence of taking drugs as examples of the Shwartzman phenomenon. Suchett-Kaye (1950) subscribes to Lewi's views. The latter authors are probably extrapolating somewhat beyond the evidence at present, but I cite them to show the extent to which Shwartzman concepts are permeating the medical field and also the possible further clinical implications of this process.

It should be clearly realized that in the presence of a generalized infection, presumably with toxins affecting the entire vascular tree, the administration of an antigen (unfortunately, usually a drug given for the treatment of the infection) to which the patient happens to be sensitive may precipitate a generalized Sanarelli-Shwartzman reaction; and indeed this may be the explanation for some of the necrotizing vascular reactions that are being seen with increasing

frequency, and which are usually attributed to a drug sensitivity of the serum sickness type.

Somewhat analogous conditions have been reported after repeated intravenous injections of typhoid vaccine. As is well known, severe reactions may develop and may even be fatal. Urbach, Goldburgh and Gottlieb (1944) report such a case as do also Love and Driscoll (1945). Both reports attribute the fatal outcome to a generalized Sanarelli-Shwartzman phenomenon, discuss the mechanism and quote the relevant literature. They point out that the risk of such a mishap is greatest when the time between the intravenous injections is 24 hours. It will be recalled that the reactive state is said to persist for from 48 to 120 hours, so that to be very safe injections should not be repeated sooner than 6 days. However, the persistence of an intense reactive state is probably not much beyond 48 hours, so that if the injection be repeated after this time the risks are less; a repetition at 24 hours is about as hazardous a procedure as can be.

At this point it might be well to consider some of the necrotic reactions that follow the administration of antisera. Ever since therapeutic antisera were first introduced, more or less severe haemorrhagic necrotic reactions have occasionally been observed, especially when the injections were repeated in the presence of a severe infection. The original and usual explanation for these accidents was that they were examples of the Arthus phenomenon. As early as 1909 Lucas and Gay collected a series of such cases and attributed the reactions to an Arthus mechanism. Many more such cases have since been reported, but in recent years it has been suggested that they might be examples of a Shwartzman rather than of an Arthus phenomenon. Kohn, McCabe and Brem (1938) were among the first to suggest this. The theory for the production of the reactions is that the infection provides the preparatory factor, and the repetition of the antiserum, essentially horse serum protein, first sensitizes and then furnishes the antigen to the sensitized host. This leads to an antibody-antigen reaction with the consequences already described. In support of this theory it has been pointed out that the repeated giving of antisera in the *absence of acute infections* has apparently not caused any such reactions. Black-Schaffer and his colleagues (1950) have shown experimentally in the rabbit that repeated administration of a potent antigen yields rather trivial lesions, but if the same material is combined with a Shwartzman filtrate much more severe necrotic reactions are obtained with fewer injections.

There are several ill-defined, poorly substantiated biological reactions that seem to be on the periphery of allergic processes for which no clear or adequate explanations have ever been given. The majority of them have been subsumed under the title of heteroallergy. The term heteroallergy then designates the altered reactive capacity of a specifically allergized organism to other or "hetero" allergens. Heteroallergic manifestations are subdivided into parallergic

and metallergic (Urbach and Gottlieb, 1946). This review will not consider these phenomena except to suggest that some of them develop on the basis of a Shwartzman reaction. The term heteroallergy embraces a medley of manifestations with different pathogeneses, so that while a Shwartzman mechanism may explain the development of some of them, it is not suggested that it explains all of the group.

A few examples of so-called heteroallergic reactions will be given. It is stated that if tuberculin-negative children are tested with tuberculin at the height of a vaccinal reaction, they will react positively at the tuberculin site. Presumably, the tuberculin acts as a skin preparatory factor in the presence of circulating eliciting toxins furnished by the vaccine.

It is reasonably well established that a tracheal superinfection of tuberculin-sensitive animals with saprophytic organisms (particularly *Esch. coli*) will yield necrotic pulmonary lesions, whereas the same procedure in normal animals gives little or no reaction. This is the observation usually quoted to justify the concept of heteroallergy, but the findings would appear to be best explained on the basis of a Shwartzman phenomenon; *Esch. coli* strains are as a rule potent Shwartzman filtrate producers.

Animals, including man, sensitized to the tubercle bacillus often show exaggerated cutaneous reactions to other micro-organismal extracts, e.g., *Esch. coli*, *Staphylococcus aureus*, *Brucella suis* (see Higginbotham, 1937). One explanation has been that all these bacteria have a common antigen; this may be so, but I do not believe this explanation is as likely as one invoking the Shwartzman phenomenon. Certain of the manifestations already discussed under Shwartzman reactions elicited by antigen-antibody unions could be classified as heteroallergic reactions.

Finally it would be well to discuss briefly some of the possible immunological approaches to an interference with the reaction of the Shwartzman phenomenon. Although the reaction does not develop, so far as is known, because of an antibody system, antibodies can interfere with or inhibit the development of lesions. It has been shown in the experimental animal that an antibody, either against the material of the preparatory filtrate or against the eliciting factor, will, if given in between the two injections, prevent or greatly reduce the necrotic reaction that would otherwise develop.

In man such a method of attack has had limited trial but where tried has seemingly been beneficial. Winkelstein and Shwartzman (1942) treated cases of ulcerative colitis with a purified and concentrated horse *Esch. coli* antiserum and obtained very favourable results. Schmidt (1936) treated a case of pyoderma gangrenosum and ulcerative colitis with a hyperimmune streptococcal serum with striking results. In this case the serum was injected directly into the cutaneous ulcer and surrounding tissues. In the cases treated by Winkelstein and Shwartzman the serum was given either intravenously or intramus-

cularly. Lest one get too sanguine about such an approach, let me point out that at least two different types of difficulties may be met. First, it may not be easy to determine which organisms are acting either as preparators or elicitors. Second, assuming the organisms responsible are identified, there may be considerable technical difficulties in obtaining adequate supplies of a potent antiserum.

SUMMARY AND CONCLUSIONS.

1. The Shwartzman reaction is described and its pathogenesis considered.
2. The similarities and dissimilarities between the Shwartzman and the Arthus reactions are pointed out.
3. The possible widespread clinical ramifications of the Shwartzman mechanism are considered. It is suggested as the underlying mechanism for a variety of dermatoses, and also as a possible explanation for the necrotic reactions occasionally seen after the injection of various antigens. Many of the somewhat bizarre manifestations that are now labelled as heteroallergic manifestations may also be of this nature.

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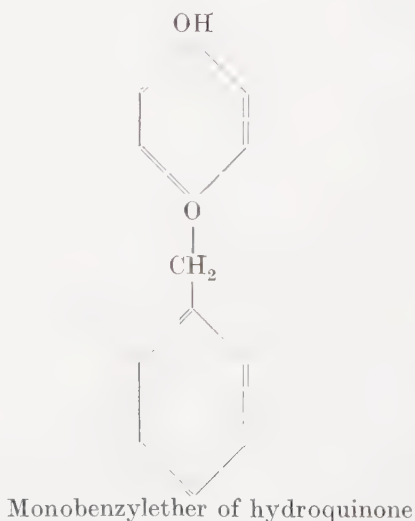
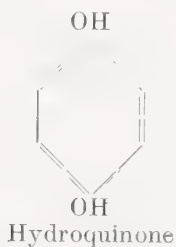
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A NOTE ON THE DEPIGMENTARY PROPERTIES OF MONOBENZYLETHER OF HYDROQUINONE

L. FORMAN.

In 1939 and 1940 Oliver, Schwartz and Warren described cases of occupational leukoderma occurring in a tannery. They were able to demonstrate that the offending substance was an antioxidant, monobenzylether of hydroquinone. This is known commercially as "agerite alba," and was added to the rubber mixture by the manufacturing company in 1937.



As rubber ages it becomes hard and brittle. The antioxidant is used to delay this change, fixing oxygen which would otherwise be available to combine with the rubber molecules. These authors were able to confirm the depigmentary action of the monobenzylether of hydroquinone by patch tests on the affected workers and these observations have been repeated on volunteers. They noted that agerite alba produced in a proportion of cases evidence of a slight dermatitis followed, within two weeks to a period of several months, by depigmentation and later by return of pigment. The skin around the follicles was the last to become depigmented and the first to show return of pigmentation, suggesting, according to Wideman(1940), that there were larger quantities of oxydase present in these areas of skin. The increased supply of oxygen would not be totally absorbed by the monobenzylether of hydroquinone.

Denton *et al.* (1952) described the results of patch tests with 10% and 30%

monobenzylether of hydroquinone applied continuously for thirty days, on five coloured and two white patients. Depigmentation developed in two of five negro subjects, the higher concentration giving greater depigmentation. With similar concentrations of hydroquinone two of five negro subjects developed slight depigmentation and two developed dermatitis, one with a secondary increase of pigmentation. No change was noted on the skin of the two white males.

The effect of hydroquinone on the skin was investigated because commercial agerite alba contains a small proportion of hydroquinone. In the workers affected by depigmentation due to the rubber gloves, patch tests with hydroquinone gave a slight degree of depigmentation in a small proportion of the patch tests. The same effect was noted in the patch tests on normals.

Sulzberger, in the discussion on Oliver *et al.* (1940), stated that hydroquinone powder was ineffective in full strength in the production of depigmentation, though it produced some skin irritation and in 50% of cases tested with the powder an eczematization occurred. Denton *et al.* (1952) demonstrated that hydroquinone injected under the skin of a black male rat produced an area of depigmentation of the hair.

Hydroquinone or quinole is widely used in photographic developers. It is well known as a skin sensitizer, but the only reference found of its ability to produce depigmentation is the case of depigmentation of the fingers of a patient described by Duffield (1952). This paucity of case reports of depigmentation of the fingers in photographers may be explained by the suggestion of Denton *et al.*, that hydroquinone is only water-soluble and therefore not easily absorbed into the skin; furthermore, it is unstable and is rapidly broken down.

Dr. Everett Fox, in the discussion on Oliver *et al.* (1940), recorded a patient whom he had treated for amoebiasis with a quinone compound (5.7. diiodo-8-hydroxyquinoline) over a period of eight months. After two to three months areas of vitiligo appeared and extended and the hair of the patient rapidly became grey—a result comparable with the feeding experiments on black guinea-pigs. When the medicament was stopped the vitiliginous areas gradually improved.

Denton *et al.* (1952) carried out *in vitro* experiments to determine the action of monobenzylether of hydroquinone on the tyrosinase-tyrosine-melanin sequence. No inhibition of oxygen uptake was shown in either the tyrosine-tyrosinase-monobenzylether of hydroquinone combination or the dopa-tyrosinase-monobenzylether of hydroquinone combination. Hydroquinone, however, blocked tyrosine conversion into dopa. They suggested therefore that in the skin monobenzylether of hydroquinone was converted into hydroquinone, or prevented the oxidation of SH groups which bind copper in the tyrosinase complex. The latter suggestion is to be preferred when one considers Muller's report quoted by Oliver *et al.* (1940) that the skin depigmented by monobenzyl-

ether of hydroquinone gave a negative dopa reaction, suggesting an *in vivo* blocking of enzyme action at a site unaffected by hydroquinone.

Agerite alba is soluble in sweat and in alkaline solution: sweat becomes more alkaline as secretion is continued. In the original cases described by Oliver *et al.*, the incidence among the workers depended upon the time the gloves were worn. Their illustrations show spread of depigmentation on the upper arms, trunk and face. The upper arms were in contact with the long gloves when the arms were bent and were touched with the gloved hands. The palms were not involved, and the dorsal aspects of the fingers largely escaped.

The early reports of the depigmentary phenomenon at once raised therapeutic possibilities but it seemed that sensitization could occur, possibly rather more readily on white skins. Certainly the speed of depigmentation might not be as fast as in the black skin, and therefore treatment would be continued for a longer period and sensitization would be more likely to be seen.

Again, Bernstein and Sachs (1949) mention one white man who developed an erythema following contact with neoprene (synthetic rubber containing monobenzylether of hydroquinone), spreading to involve the forearms and the face. The erythema was followed by an increase in pigment until the affected sites became almost black. A patch test produced erythema and pigmentation.

To estimate the risk of sensitization Denton *et al.* used 20% concentration of agerite in a vanishing cream base on the forearms of 70 normal subjects patch-tested for 48 hours: no case of sensitivity was noted. Using a stronger concentration of the powder itself Sulzberger noted the development of a dermatitis and recorded the substance as capable of producing a true allergic response. He found that agerite alba powder produced depigmentation in 17 of 18 negroes. Using diminishing concentrations he did not find a parallel in the degree of irritation produced and the degree of depigmentation.

Denton *et al.* recorded the result of treatment of a case of generalized lentiginos with marked improvement over the face. One hand was treated and showed a favourable contrast to the untreated hand. A second case showed only slight depigmentation. They also treated with success a case of chloasma following pregnancy with 30% ointment and a case of macular pigmented naevus treated with 3% monobenzylether of hydroquinone daily for two months with resulting depigmentation. Fitzpatrick (personal communication, 1953) believes that 5% agerite in a water-soluble base could be applied two to three times a day and should be reasonably safe, used 1-4 months. Should the pigmentation be not obviously diminished, then the treatment should be stopped. Signs of any irritation or sensitivity should be looked for carefully. Peck and Sobotka (1941) stated that monobenzylether of hydroquinone could produce a depigmentation without a pre-existing dermatitis.

The following is a note on a case of chloasma treated with monobenzylether of hydroquinone:

Miss C. W—, aged 33 years.

The patient noticed the pigmentation of forehead and cheeks three years ago. Her periods have been normal. There was no particular disturbance, mental or physical, with which she could associate the onset of the pigmentation.

She had also a large, semi-pedunculated plaque on the back of the scalp. Biopsy showed this to be a benign melanoma.

She applied an ointment containing 5% monobenzylether of hydroquinone once a week for five months to the left side of the forehead, and for three months to all areas. No inflammatory reaction occurred, but depigmentation was definite. (The patient was shown at the Royal Society of Medicine, London, on 19 February 1953.)

To sum up: (i) Monobenzylether of hydroquinone has a specific blocking action on the formation of skin pigment, perhaps at the dopa—melanin stage.

(ii) The compound can also act as a skin sensitizer. The depigmentary and sensitizing properties do not appear to run parallel.

(iii) On white skin a dermatitis caused by this chemical may be followed by increase of pigmentation.

(iv) A case of chloasma is presented which has depigmented following the application of the monobenzylether of hydroquinone without evidence of any dermatitis.

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CAMPTODACTYLIA (LANDOUZY) WITH OTHER NAEVI.

W. E. ALDERSON.

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A MAN aged 27 ; a display artist.

History.—He first remembers contracture of the fingers and toes developing after measles at the age of 6 years. There has been neither pain nor inflammation of the joints. The contractures do not inconvenience him and he is able to ride a motor cycle.

At the age of 18 years he noticed brownish areas developing on both forearms which became more hirsute than normal. At the same time reddish areas were noticed on his shoulders, thighs and lower abdomen. The affected parts of the anterior aspects of the thighs were also more hairy.

There is no history of trauma or friction.



FIG. 1.

Family history.—Nil.

On examination.—A thin young man. There is bilateral symmetrical permanent flexion of the interphalangeal joints of fingers and toes (Fig. 1). The metacarpo- and metatarso-phalangeal joints are not affected. The flexion is partial ; extension is impossible but further flexion can be obtained.

On the extensor aspects of both forearms are pigmented hairy naevi. On the shoulders, thighs and lower abdomen are capillary haemangiomas with hirsutism of the affected areas on the thighs.

Neurological examination (Dr. Rae).—Normal.

Histology (hairy part of left arm).—The section shows only a few of the basal cells to be pigmented, and a few melanophores in the dermis. Apart

from a few small perivascular round-cell collections in the dermis, nothing abnormal was seen.

Comment : The term Camptodactylia was first used by Professor Landouzy in 1885.

Photographs of this patient were sent to Dr. F. Parkes Weber for his opinion. He regarded the case as a congenital or early developmental type of camptodactylia allied to one that he had described in association with multiple superficial naevi which, in his particular case, were of the Rendu-Osler type of telangiectasia (1938, 1947).

An orthopaedic surgeon, Mr. Wishart, has suggested arthrodesis of the proximal phalangeal joint of a fifth finger ; if that is successful he will perform it on the other fingers. This would improve the appearance about which, however, the patient is not unduly sensitive.

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ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY

President—Dr. G. B. DOWLING.

19 February 1953.

Mycosis Fungoides.—Dr. I. B. SNEDDON.

A. W—, male, aged 66 ; monumental mason.

History.—In October 1952 he developed an itching red eruption on the head, face and neck and his face became swollen. Apart from this he felt well : he had taken no drugs. The rash had spread slowly down his trunk and the proximal parts of the limbs.

Past history and family history.—Not relevant.

On examination.—A confluent bright erythema was present over the scalp and face : the skin of the face was indurated and deep fissures were present in the natural skin folds around the mouth. The neck, upper trunk and arms showed a discrete red follicular papular eruption which was becoming confluent around the neck (Fig. 1). The hands and feet were unaffected. No enlargement of lymph glands, liver or spleen could be found.

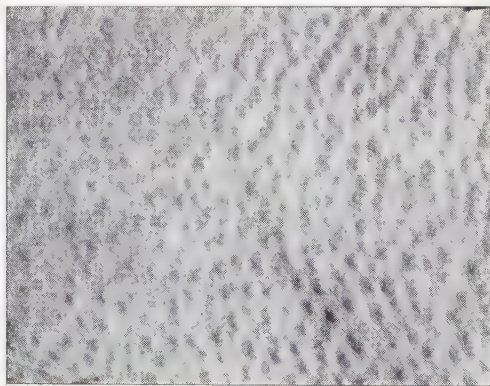


FIG. 1.—The skin of the upper trunk showing the follicular papular eruption.

Investigations.—Skiagram of chest showed no significant abnormality. W.R. negative. Blood count : Haemoglobin 128% ; red cells 6,400,000 ; leucocytes 9000 ; differential count normal ; marrow puncture within normal limits.

Histological examination of the follicular rash on the trunk (Dr. L. C. D. Hermitte) : The epidermis shows a slight degree of acanthosis. Its surface is wavy but there is no hyperkeratosis or parakeratosis. The mouths of the follicles are, however, filled with lamellated keratin. There is a dense perifollicular infiltrate with lymphocytes and histiocytes and the centre of the follicle appears to contain keratin. The sebaceous glands show some degree of atrophy. Some of the capillaries in the corium are dilated and surrounded by a few chronic inflammatory cells. The appearances suggest a mild degree of pityriasis rubra pilaris.

Histological examination of the skin of the face (Figs. 2 and 3) shows oedema and degeneration of the corium, which is densely infiltrated with round cells. This infil-

trate is pleomorphic in character. Some of the cells are small with dark nuclei, others are larger with pale nuclei, many showing mitotic figures. These cells appear to be reticulum cells. The infiltrate has invaded the epidermis in several places. The appearances are those found in a malignant reticulosis.



FIG. 2.—Section of facial skin. $\times 43$.

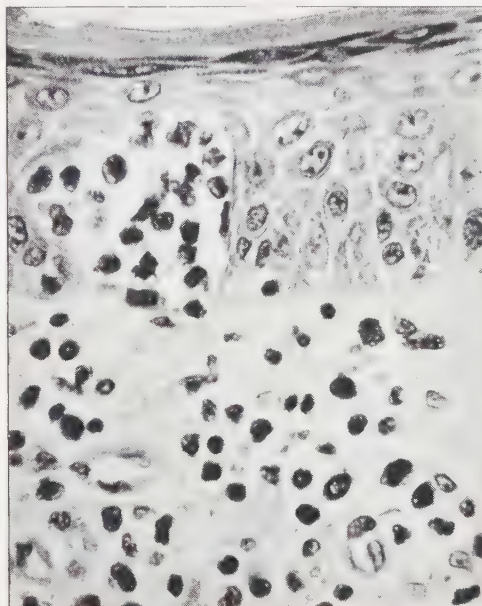


FIG. 3.—Section of facial skin. $\times 460$.

Comment.—Although the infiltrate does not show much pleomorphism, its diffuse arrangement and the clinical picture of a reticulosis so far confined to the skin suggests a diagnosis of mycosis fungoides in the erythematous and infiltrative stage. That mycosis fungoides can present with a seborrhoea-like eruption is well known, but that it can simulate pityriasis rubra pilaris so closely has not, so far as I know, been described. I have watched a similar case for five years; this case has been controlled with cortisone 250 mg. daily for two years. He has never shown any evidence of systemic involvement, nor has the large dosage of cortisone had any apparent harmful effect.

The PRESIDENT: The diagnosis of a reticulosis appears to be beyond dispute but I do not believe that the skin reticuloses presenting as a diffuse erythrodermia are as yet accurately sorted out. Mycosis fungoides may perhaps not be the correct term for this case.

Dr. SNEDDON, in reply to a question: In my previous case x-rays had no beneficial effect, and in the present case a total of 450 r has been given to the right side of his face without any benefit.

? Purpura Urticans with Regional Distribution (Early Manifestation of Vascular Sensitization) and Polyarthritides. Case for Diagnosis.—Dr. L. FORMAN.

M. R—, female, aged 43.

In October 1950 small urticarial papules appeared over the ankles and have since involved the legs, thighs, buttocks, face, the exposed parts of the chest, the hands and arms. She has always had a high facial colour, but during the past few years the colour has deepened and telangiectasia of the face and of the chest wall is more

obvious. Over the areas affected red macules appear which quickly become urticated to form prominent white papules of a diameter of 1 cm., showing a central red punctum, presumably a dilated capillary. They do not itch, but burn, and are slightly tender to touch. After two to three days the papules subside, leaving a brown stain which may take up to a week to disappear. All stages are to be seen on the limbs. There has also been an associated periodic swelling and pain of the hands with some tenderness of proximal joints of the thumbs and swelling of the ankles, knees and elbows. The papules are increased in number before the period is due. She was put in bed in hospital and obtained much relief. While at rest in bed the number of papules and their duration have diminished. Cold and fatigue, she believes, increase the number of papules.

Investigations.—Effect of cold: Hand immersed in cold water (16° C.) for ten minutes: numerous papules developed on the hand and on the arm; during the next three hours all finger-joints swelled and numerous papules appeared on the arms and legs.

Effect of heat: Feet immersed in hot water for ten minutes: no effect on papule formation.

Histamine scratch produced a flare and also a flare around papules 2 cm. away. The reaction lasted for three hours. (Reaction in control normal individual lasted twenty minutes.)

Electrophoresis with 0.05% carbachol showed greater sensitivity than normal.

No cold agglutinins were detected in the blood.

No urinary porphyrins; bone-marrow normal, no L.E. cells.

Blood count normal. W.R. negative.

Blood: congo red elimination test within normal limits.

Serum cholinesterase within normal range.

In 1951 there was dental sepsis of the upper teeth with alveolar loss. This was treated.

Histology of a papule: Dilatation of superficial capillaries with oedema. The cellular exudate consists of pyknotic polymorphs and a few histiocytes and eosinophils and red cells. ? Homogenization of subepithelial layer of deeper vessels.

Treatment.—Antihistamines and elimination diets without avail.

Comment.—The recurrent urticarial wheals, with residual staining probably due to the diapedesis of red cells seen in the section and the recurrent transient peri-articular swelling suggest an allergic reaction. No food or drug allergens could be detected. The superficial capillaries may be the site of sensitization. At the moment there is no sign of vascular damage to larger blood vessels or to the renal blood vessels. The biopsy, with its large number of polymorphs suggesting an abscess, recalls the histology of erythema elevatum diutinum which, as has been shown, is associated with degenerative changes in the skin blood vessels.

Addendum (10.iv.53).—She had ACTH gel 20 mg. a day for seven days intramuscularly and then ACTH 20 mg. a day intravenously for seven days, and the third week she was given ACTH gel intramuscularly 20 mg. per day for seven days. During the course of treatment the patient had no further swelling of the joints, the maculopapular rash gradually disappeared and the duration of the papules was limited to six hours: there was no subsequent pigmentation. The venous congestion of the face and chest also diminished. She has been observed for the past two weeks, since the cessation of treatment, and she has again developed a few small papules on the limbs.

Dr. H. HABER: The histology reminds me of the case which Dr. Brian Russell and I showed (1950, *Proc. R. Soc. Med.*, 43, 560). I would regard that condition as belonging to the group of erythema elevatum diutinum. The perivascular infiltration consisting of polymorphs and a few eosinophils with very little degeneration of the cells is unique and characteristic of erythema elevatum diutinum as outlined by Weidmann.

Widespread Morphoea with Bullae and Leukoplakia.—Dr. R. E. CHURCH
(for Dr. I. B. SNEDDON).

D. R—, a man, aged 40, was in good health until the winter of 1944, when for the first time in his life he developed severe chilblains on the fingers which persisted for two months. These have never recurred, and there have been no attacks of Raynaud's phenomenon.

In 1945 three patches of morphoea appeared on his back, and fresh patches have appeared since, and spread over wide areas of his trunk and limbs. Ulcers appeared on the back 3 years ago, and in the past few months these spread so widely that he became bedridden.

The ulcers occasionally start as fissures in the morphoeic areas but mostly begin as bullae which become haemorrhagic and finally rupture. They usually form in the middle of the patches of morphoea and many have appeared on the abdomen.

For the past two months he has noticed soreness of the tongue.

There have been no other symptoms and there is no relevant past history or family history.

Examination.—A typical patch of ivory-white morphoea with a violaceous edge involves the left eyelid. Similar discrete ringed lesions are present on the shoulders. A complete necklace of morphoea encircles the neck and has caused alopecia where the hair margin has been invaded in the occipital area. The arms and backs of the hands are almost completely covered with confluent lesions, a few of which have ulcers at their centres. Both elbows are contracted. The trunk and thighs are completely ensheathed over a vest and pants distribution in scleroderma, which also extends over the penis. At the edge of active areas is a typical violaceous areola. Over large areas of the back and abdomen the sclerodermatous infiltration has subsided, leaving guttate pigmentation and telangiectases with atrophic skin resembling x-ray burns. Circinate red healing scars of bullae about 2 cm. in diameter are dotted over the abdominal wall. Over both legs and the dorsum of the feet are figurate areas of morphoea, and in the middle of many areas are ulcers and the scars of healing ulcers.

Mouth.—On the left buccal mucosa is a delicate white leukoplakic area. The tongue is scarred on the right side and slightly bound down. In that area and on the dorsum there is a leukoplakic appearance.

Investigations.—Skiagrams—Chest: There is no evidence of disease of the chest. Barium swallow: No evidence to suggest sclerodermatous change of the oesophagus. Follow through: Shows no evidence of any involvement of the gastro-intestinal tract by scleroderma. Hands: No evidence of bony lesion or calcinosis.

Creatinin excretion 0.96 g./24 hr. specimen of urine.

Creatin excretion 0.19 g./24 hr. specimen of urine.

Electrocardiogram normal.

Wassermann reaction negative.

Histology.—Skin:—The section shows thinning of the epithelium with a patchy chronic inflammatory infiltrate. There is atrophy of the skin appendages due to a great overgrowth of acellular collagen fibres in the corium. The appearances are those of morphoea.

Muscle (left biceps) normal.

Buccal mucosa: The epithelial layer is thin and there is a light inflammatory infiltrate mostly of lymphocytes and histiocytes just beneath the epidermis. The basal layer is slightly irregular and shows fairly numerous mitoses. The appearances are those of leukoplakia. The subepidermal collagen is dense, but does not obliterate the capillaries as would have occurred in scleroderma. Fatty tissue and muscle fibres are also to be seen in it.

DISCUSSION.

Unlike generalized scleroderma, morphoea is extremely uncommonly associated with lesions of the internal organs. There is one report of gastro-intestinal stenosis associated with morphoea (Pinker and Braun, 1950), and several of associated calcinosis. The present case has such unusually severe skin lesions that we searched for evidence of systemic involvement but without success.

Most reported cases of morphoea involving the buccal mucosa have had the *coup de sabre* type of lesion, but Gougerot and Eliascheff (1933) reported a case with a mucosal lesion associated with widespread skin lesions. In all cases the mucosal lesions have been discrete white plaques sometimes with a violaceous edge and have shown the histological changes of morphoea. In this case, although the tongue appears scarred the lesions are clinically and histologically those of leukoplakia.

Ulceration in morphoea is uncommon, but several cases have been reported. Bullous localized scleroderma appears to be very rare.

Templeton (1941) published one case and cited one other of widespread morphoea with bullae. In both, as in the present one, bullae were most commonly seen on the abdomen. He concluded from a study of the histology that the bullae were formed subepidermally and arose from lymph stasis and oedema.

Bullae are quite common in lichen sclerosus et atrophicus, which many consider to be merely a superficial variant of morphoea. Anderson (1944), reviewing the past cases of bullous scleroderma, concluded that the majority were lichen sclerosus, but the present case illustrates the possibility that the original authors were correct in their diagnoses of morphoea.

REFERENCES.

- ANDERSON, C. R. (1944) *Arch. Derm. Syph.*, **49**, 423.
 GOUGEROT and ELIASCHEFF, O. (1933) *Bull. Soc. Franç. Derm.*, **40**, 111.
 PINKER, VON H., and BRAUN, H. (1950) *Deutsche med. Woch.*, **75**, 113.
 TEMPLETON, H. J. (1941) *Arch. Derm. Syph.*, **43**, 361.

The following cases also were shown :

Dermatofibrosarcomata Protuberans.—Dr. E. WADDINGTON.

Chloasma Treated with Monobenzyl Ether of Hydroquinone.—Dr. L. FORMAN (see p. 406).

? Secondary Carcinoma. ? Amelanotic Melanoma.—Dr. S. C. GOLD.

Parakeratosis Variegata with Unusual Features.—Surg.-Lt.-Cdr. R. SCUTT.

Reticulosis Cutis.—Dr. N. A. THORNE (for Dr. BRIAN RUSSELL).

Syphilitic Leukoderma of the Neck.—Dr. C. S. NICOL.

Congenital Progressive Cutaneous Atrophy with Bullous and Poikiloderma-like Manifestations.—Dr. THERESA KINDLER.

Familial Benign Pemphigus.—Dr. C. D. CALNAN.

Two Cases of ? Pigmented Purpuric Lichenoid Dermatitis (Gougerot and Blum).—Dr. B. SCHWARTZ.

NORTH BRITISH DERMATOLOGICAL SOCIETY.

Glasgow, 13 March 1953.

Diffuse Pigmentation.—Dr. G. LESLIE.

A man aged 53, an unemployed labourer.

History.—The patient first came to the medical dispensary complaining of "black-outs" followed by sweating, and dyspnoea on exertion. A diffuse brownish-black

pigmentation of the whole body and mucous membranes had been present for many years. There is no history of arsenical therapy and he has never worked with any tar products. He was at one time an actor and used a considerable amount of make-up on his face and neck, areas where the skin is nearest to normal in colour.

On examination.—The pigmentation is particularly deep in the groins and in the axillae.

He is well nourished and his weight has remained steady over many years. He is not negroid in appearance. He is of low intelligence. No lice could be detected either on his body or on his clothes.

The heart shows some left ventricular enlargement (B.P. 200/105), and careful examination of the other systems reveals no abnormality.

Blood W.R. negative.

Skiagram of the chest : normal.

Histology.—There is slight hyperkeratosis and thinning of the prickle-cell layer, and a definite increase in pigmentation in the basal layer. Clear cells are not excessively numerous. Pigment is also present in the corium, both intra- and extra-cellular.

Comment.—Trueblood in 1947 reported a case of diffuse pigmentation, the patient ultimately becoming black. This followed upon the surgical removal of a pigmented, hairy birthmark. He was able to find two similar cases in the literature.

REFERENCE.

TRUEBLOOD, D. V. (1947) *Northwest Med.*, **46**, 199.

Naevus of Face.—Dr. THOMAS COCHRANE.

A schoolgirl aged 11 years.

The patient has had a large pigmented naevus on the right side of her face since birth. The naevus increased in size with the patient. She came to me on 13.ix.52 as she and her mother were worrying about its size and the disfiguring deep brown colour.

As there is a long waiting list for plastic surgery for the removal of these naevi it was decided to treat the lesion with an ointment containing 33% monobenzyloether of hydroquinone in lanolin. This substance was found to depigment the hands of workers wearing rubber gloves and has been used in the treatment of chloasma.

The patient used the ointment daily from 13.x.52 to 16.i.53 with no untoward reaction, and an excellent cosmetic result has been obtained. All the deep brown staining was removed and the skin, unless examined at very close range, now appears normal in colour and texture.

From 16.i.53 to 10.iv.53 she used the ointment only occasionally and since that date none has been applied.

Postscript.—There has been no reappearance of pigmentation six weeks after stopping the ointment.

The following cases also were shown :

Keratoderma Punctatum.—Dr. FERGUSON SMITH.

Scleroderma with visceral manifestations ; Primary Tuberculous Complex.—Dr. T. COCHRANE.

Premycosis ; Necrobiosis Lipoidica Diabeticorum ; ? Reticulosis.—Dr. J. O'D. ALEXANDER.

Systemic Lupus Erythematosus (treatment with cortisone) ; ? Hodgkin's Disease ; Erythema Annulare Centrifugum.—Dr. G. LESLIE.

Bazin's Disease and Erythema Nodosum.—Dr. T. PASIECZNY.

NORTH OF ENGLAND DERMATOLOGICAL SOCIETY.

Bradford, March 1953.

Longitudinal Linear Pigmentation of Nails.—Dr. A. Bigham.

A woman aged 22.

A young married woman presenting longitudinal bands of pigmentation on the following nails: Right thumb, index, middle and ring fingers (Fig. 1); left index; right fourth toe; left second toe. The bands are of a faint brown colour and uniform width, affecting the central areas of the nails, one band to each nail.

The condition is of fifteen months' duration, and commenced during the first three months of her first pregnancy. The pregnancy terminated in a stillbirth about the seventh month. Up to that time the pigmentation had been increasing in depth of colour, but after parturition there was a gradual fading in its intensity.



FIG. 1.

There is no other pigmentary anomaly, and the family and previous medical history is normal. The patient has just become pregnant again.

The following cases also were shown:

Lipomata; Xanthoma Tuberosum; Adenoma Sebaceum; Tinea; Lupus Erythematosus; Congenital Nail Dystrophy.—Dr. W. E. ALDERSON.

Occupational Koilonychia and Onychorrhexia; Morphoea; Leucoderma Treated with Meladinine; Nodular Non-Suppurative Panniculitis.—Dr. C. I. BARROW.

? Parapsoriasis; Urticaria Pigmentosa; Case for Diagnosis Separation of Nails; Pili Torti; ? Elephantiasis Nostris; Hyperkeratosis Palmaris et Plantaris; Darier's Disease; Pemphigus Vulgaris; Necrobiosis Lipoidica; Ulcus Cruris; Xanthelasma Palpebrarum in 3 Sisters; Senear-Usher Syndrome; ? Reiter's Syndrome.—Dr. ALLAN BIGHAM.

BOOK REVIEWS.

LEPROSY.*

THIS book is intended not for leprologists but for students and dermatologists. It is a concise and very readable account of the malady by a dermatologist practising in Hawaii where leprosy is endemic. The print is large and clear, the illustrations are good and the flexible covered book slips easily into a pocket. It can be recommended to those who seek to get clear ideas about leprosy, but those who live in the sterling bloc will probably find Muir's *Manual of Leprosy* better value for their money.

G. W. B.

AN AMERICAN FORMULARY.†

THIS small book is presented as a model dermatological formulary based upon the composite experiences of the leading teachers of dermatology in the U.S.A., the Americas and Europe.

It is divided into three sections, the first of 72 pages being concerned with topical remedies and containing many useful details of their indications and methods of application. The second section devotes 42 pages to systemic therapy and is subdivided into (a) Medicaments for Oral Use and (b) Medicaments for Parenteral Use. The third section consists of 6 pages listing the test antigens, caustics, dressings, local anaesthetics, freezing and cleansing agents commonly used in the clinic. A fully comprehensive index of 18 pages completes the volume.

The formulary is thus very complete and closely resembles the pattern of our own prescribing, but it is probably less critical and it includes many proprietary preparations. The latter may be inevitable in the cases of new drugs or patented bases, but near imitations of standard formulae scarcely justify inclusion.

The use of bentonite in shake lotions will be noted with interest since this substance is now widely used over here, and menthol is evidently more popular as an antipruritic agent. Oil-in-water emulsions of Burow's solution with additions of phenol, menthol and tar present a useful range described as soothing, antipruritic and astringent. Carron oil was an emulsion of linseed oil and lime water and it would surely be better to describe the modified form as olive oil or lime water emulsion. Similarly "Dalibour solution (modified)" is not *l'eau d'Alibour* in spelling or constitution and might more simply be called "sulphate of copper and zinc solution."

An interesting feature of this formulary is the inclusion of many details of the indications and methods of applying various topical applications as well as brief directions to the patient for the treatment of scabies, pyoderma and acne, and for the use of wet dressings.

Dermatologists will welcome this concise volume of dermatological experience in therapy from the New York Skin and Cancer Unit for there is much of interest and value in it.

R. T. B.

* *Modern Concepts of Leprosy*. By HARRY L. ARNOLD, Jr., M.D. Oxford: Blackwell Scientific Publications, Ltd. Pp. 105. 33 illustrations. Price 27s. 6d.

† *Dermatologic Formulary*. By FRANCES PASCHER. New York: Paul B. Hoeber, Inc. Pp. 150. Price \$3.00.

MANUAL DE MICOLOGIA MEDICA.*

THIS is a useful text-book written in Spanish for medical practitioners and students. In three introductory chapters on general mycology, the morphology, classification and biology of fungi are discussed. Numerous media and technical methods are described under a general heading and also with various diseases where their use is applicable. The tinea infections are subdivided under superficial mycoses to a degree which results in some loss of uniformity of diagnostic approach. Of the chapters describing deep mycoses, those dealing with South American blastomycosis and mycetoma are particularly detailed and represent much personal experience of these infections.

The terminology used is similar to that generally adopted in Britain. *Cohnistrepthrix* is, however, preferred to *Actinomyces*, and *Nocardia* is not used as a generic name for the aerobic Actinomycetes. *Actinomyces gypsoides* is given as a species distinct from *A. asteroides*, rather than as a variant. A helpful summary is made of the mycotic diseases affecting various special systems. The bibliography is classified and comprehensive; it contains reference to much recent South American work.

On the whole, the quality of photographs is poor, particularly the reproduction of radiographs, and scales of magnification are not appended to photomicrographs.

Throughout the volume, quotations, tables and illustrations are taken from numerous text-books and papers, providing much useful immediate reference material.

R. W. R.

MEDICAL MYCOLOGY.†

DOCTORS MOSS and McQUOWN have prepared this atlas from their teaching material at the Charity Hospital, New Orleans. Their experience is wide and they summarize the important diagnostic features of the various mycotic diseases concisely. Dermatological features of each disease are given some consideration, but the sections on Immunology and Formulary could well have been omitted from an atlas of this kind.

Other criticisms of the text concern matters of terminology and detail. The term dermatophytosis would perhaps have been better limited to ringworm infections rather than used to include infections by *Candida albicans*. The uncertainty which exists about so-called cultures of *Nocardia tenuis* and *N. minutissima* might have been expressed more definitely. The authors lay unusual emphasis upon the value of Littman's oxgall agar for primary cultures since contaminants were found to be minimal on this medium.

In their desire to achieve a complete clinical, mycological and pathological study, they have included photographs which would help very little in diagnosis, and a number of others fail to demonstrate what is required of them. A bibliography devoted specifically to technical and diagnostic papers would have been of value.

R. W. R.

* *Manual de Micologia Medica*. By CARLOS DA SILVA LACAZ. Sao Paulo: "Liteci." Pp. 370. Figs. 116.

† *Atlas of Medical Mycology*. By E. S. MOSS and A. L. McQUOWN. London: Baillière, Tindall & Cox. Pp. 246, 248 illus. Price 61s. 6d.

CURRENT LITERATURE

NAEVUS FLAMMEUS TARDIVUS. INGBORG NIEMAN-ANDERSEN. (1952) *Z. Haut- u. Geschlkr.*, 12, 251.

A 26-year-old man developed a naevus flammeus in the left trigeminal region following exposure to severe cold, but since birth he had had a pinhead-sized haemangioma below the left eyelid. The author considers that the naevus flammeus development was due to the activation of an embryonal rest by the cold stimulus.

P. D. C. K.

SCLERODERMA AND SCLEROSIS OF THE INTERNAL ORGANS. W. RUBE. (1952) *Z. Haut- u. Geschlkr.*, 13, 45.

Microscopic and clinical findings in a case of scleroderma with lesions of the pituitary, thyroid, suprarenals, liver and lymph glands with a survey of the literature and a discussion on the pathogenesis of scleroderma.

P. D. C. K.

LYMPHOCYTOMA AND ITS TREATMENT. HEINZ WALTHER. (1952) *Z. Haut- u. Geschlkr.*, 13, 136.

A case of the solitary infiltrative type of lymphocytoma, with special reference to the histology and a review of the literature. The lesion healed after administration of 2.8 million units of penicillin.

P. D. C. K.

CONNECTIVE TISSUE NAEVUS WITH HYPERTRICHOSIS. HEINZ WALTHER. (1952) *Z. Haut- u. Geschlkr.*, 13, 139.

A 26-year-old man with a connective tissue naevus in the left sternal region with marked hypertrichosis in the same area. The author concludes that the hypertrichosis was due to abnormal vascular innervation as in hypertrichosis neurotica.

P. D. C. K.

THE VALUE OF RADIOTHERAPY IN MYCOSIS FUNGOIDES. H. J. HEITE. (1952) *Z. Haut- u. Geschlkr.*, 13, 174.

The statistical evaluation of 153 cases of mycosis fungoides in the literature. The author concludes that the beneficial affect of radiotherapy is slight and variable.

P. D. C. K.

THE ACTION OF STRONTIUM SULPHIDE DEPILATORIES. H. C. FRIEDERICH. (1952) *Z. Haut- u. Geschlkr.*, 13, 178.

The effects of strontium sulphide in powder form was studied in skin sections. The hairs were damaged in the distal and medial thirds of the intra-follicular segment in contrast to the thiolglycol cream depilatory, in which the hair within the follicles was unaffected.

P. D. C. K.

HAEMANGIECTASIA HYPERTROPHICANS—PARKES WEBER. FERDINANDO ORMEA and MODESTO DEPAOLI. (1952) *Z. Haut- u. Geschlkr.*, 13, 195.

One case with pictures. The author considers that the three main features, hypertrophy, over-development of the blood-vessels and naevi of various types can be distinguished even in the presence of congenital hypertrophy, and that haemangiectasia hypertrophicans is a clinical entity but that *formes frustes* exist.

P. D. C. K.

THE TREATMENT OF SKIN T.B. WITH PARA-AMINOSALICYLIC ACID. F. ZELLER. (1952) *Z. Haut- u. Geschlkr.*, 13, 207.

An analysis of 32 cases treated with P.A.S. Though the total and daily dosage given was higher than that recommended by other authors, yet the results were worse. Internal medication usually produced some improvement; adjuvant local application of P.A.S. was not impressive. Signs of intolerance were flatulence, loss of appetite, vomiting, headache and diarrhoea.

P. D. C. K.

MYXOMATOSIS CUTIS PAPULOSA. ERICH LANGER and WOLFGANG PURSCHEL. (1952) *Z. Haut- u. Geschlkr.*, 13, 235.

Case-history with pictures of a female, 52 years old, with pea-sized colourless or brownish non-irritant, firm or hard papules distributed mainly in the areas subject to trauma—the backs

of the hands, elbows, knees, thighs, shoulders and upper arms. Microscopically the corium was thickened by myxomatous deposit. The authors conclude that there was a functional disturbance of the thyroid, pituitary and associated hypothalamus with derangement of the hyaluronic acid and hyaluronidase. They consider myxomatous cutis papulosa a more appropriate description of this case than myxoedema papulosum. Kinetin, a hyaluronidase preparation, was injected into each papule once or more. The softer papules disappeared, leaving pigmentation after a few days, but the harder ones were unchanged. P. D. C. K.

INTRAVENOUS PROCAINE TREATMENT OF SKIN DISORDERS. G. WEISENBERG. (1952) *Z. Haut- u. Geschlkr.*, **13**, 293.

A review of 64 cases from 15 to 86 years old treated with intravenous injections of 0.05 procaine, 0.0025 nicotinic acid, 0.025 phenylethyl barbituric acid, and 0.00015 atrophine sulphate (mg.) in 5 c.c. ampoules. Initial dose 5 c.c. continuing with 10 c.c.; the highest single dose given was 20 c.c. The injections were given daily in most cases, but sometimes on alternate days with the patient in the prone position and at the rate of 1 c.c. per minute. In 9 cases there was a mild sensation of uneasiness, flushing, sweating or disturbed sleep. In most cases the marked sedative and antipruritic effect accelerated the healing of the disorder, especially in the older patients. P. D. C. K.

TREATMENT OF SKIN T.B. WITH ISONICOTINIC ACID HYDRAZIDE. K. LUCIUS. (1952) *Z. Haut- u. Geschlkr.*, **13**, 367.

A review of 45 cases, 32 outpatients treated with Neoteben 3 to 10 mg. per kilogramme body-weight and 13 hospital cases with Rimifon given daily for an average period of 6 to 8 weeks. Despite the varied dosage no great difference in therapeutic affect; there were no serious complications. The author is of the opinion that vitamin D₂ and isonicotinic acid hydrazide are equally beneficial. P. D. C. K.

ATABRINE IN THE TREATMENT OF DISCOID LUPUS ERYTHEMATOSUS. J. A. CRAMER and G. M. LEWIS. (1952) *J. invest. Derm.*, **19**, 393.

TREATMENT OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS WITH ATABRINE. G. C. WELLS. (1952) *J. invest. Derm.*, **19**, 405.

THERAPEUTIC ASSAYS OF THE SKIN AND CANCER UNIT OF THE NEW YORK UNIVERSITY HOSPITAL. ASSAY VII: QUINACRINE HYDROCHLORIDE (ATABRINE HYDROCHLORIDE) FOR CHRONIC LUPUS ERYTHEMATOSUS. H. H. SAWICKY, N. B. KANOF, M. G. SILVERBERG and M. BRAITMAN. (1952) *J. invest. Derm.*, **19**, 397.

Here are three reports on mepacrine in the treatment of L.E., and on the whole enthusiastic though bringing faint rumours of haematological catastrophe. Sawicky *et al.* give the numbers on their patients' sheets; but for no reason that is obvious because they clearly do not enable the reader to place the cases in chronological order. But if Wells's cases are in order of their coming under treatment then, if we say c for cured, i for improved, s for unaltered, and w for worse, his list gives the sequence c c i c i c i c i s s w. Most of us have had longer runs of success than this, though perhaps not so high a proportion of complete cures.

It appears that priority for mepacrine belongs to Popoff and Kutinscheff (1941) of Sofia.

J. H. T. D.

INVESTIGATIVE STUDIES ON COLORADO SHALE OIL. R. BRANDT and H. DEXTER. (1952) *J. invest. Derm.*, **19**, 409.

Is shale oil more carcinogenic than crude gasworks coal tar? Incomparably, no! Then is it as effective in the treatment of eczema? With all due allowance for novelty, better! Does eczema confer immunity to tar cancer? Maybe a fruitful speculation. J. H. T. D.

STUDIES OF SKIN REACTIONS TO PROPYLENE GLYCOL. T. G. WARSHAW and F. HERRMANN. (1952) *J. invest. Derm.*, **19**, 423.

Propylene glycol having been used successfully in the bases of various local remedies was therefore supposed to be non-irritant, and that is how it came to be used as a diluent in patch-testing. This investigation is the consequence of some adventitious reactions.

Briefly propylene glycol irritates only by virtue of its hygroscopic action. But the reviewer is not going to spoil the pleasure of those who can find time to read this delightful paper in the original! Anyone who is at all interested in this sort of problem will find not only a model for his researches, but many valuable and original ideas about patch-testing. J. H. T. D.

STUDIES ON THE CHEMICAL COMPOSITION OF HUMAN HAIR-FAT. I. THE SQUALENE CHOLESTEROL RELATIONSHIP IN CHILDREN AND ADULTS. N. NICOLAIDES and S. ROTHMAN. (1952) *J. invest. Derm.*, **19**, 393.

Guinea-pigs shed their hair on application of human sebum to the skin. Boys' hair contains less squalene than that of adults, but women's hair more than that of men. Since, however, no attempt was made to differentiate between the bald and the plain varieties of men, and since the fat was collected from bulked hair clippings, it is possible that the sample was more representative of the plain (or the more handsome, whichever way you like to look at it) variety of man than of the bald. On the other hand, the material had been derived from convicts (in order to avoid contamination with brilliantine, etc.), the male variety of whom naturally have more frequent hair-cuts and shampoos than the female: for in the one it is a disciplinary exercise and in the other a luxury.

J. H. T. D.

AN UNUSUAL FINDING IN EPIDERMOPHYTON FLOCCOSUM. P. McCORMACK and R. W. BENHAM. (1952) *J. invest. Derm.*, **19**, 315.

Tightly coiled spirals are occasionally found in culture preparations of *Epidermophyton inguinale*.

J. H. T. D.

ISONICOTINYL HYDRAZINE (RIMIFON) IN THE TREATMENT OF LUPUS VULGARIS: REPORT OF A CASE. M. E. OBERMAYER, J. W. WILSON and P. N. SMITH. (1952) *J. invest. Derm.*, **19**, 311.

"... has been apparently cured ... only a moderate degree of scaling and slight erythema persists ... " Lupus is of course a great rarity in the sunny west.

The patient developed an icterus index of 11 units, lost 4 lb. in weight and some of his haemoglobin concentration: otherwise he now appears well.

J. H. T. D.

THE INFLUENCE OF ACTH AND CORTISONE UPON EXPERIMENTAL ACHORION QUINCKEANUM INFECTION AND UPON ANAPHYLAXIS IN GUINEA-PIGS. F. REISS and L. CAROLINE. (1952) *J. invest. Derm.*, **19**, 365.

Favus is said to run a predictable self-limiting course in guinea-pigs. ACTH, whether given before during or both, has no influence, but cortisone prolongs the course of the first infection. But the end-point cannot be very sharp because an umpire had to be called in to guess how they were getting on.

Neither hormone influences immunity. Prolonged premedication with ACTH may have some slight influence in anaphylaxis.

J. H. T. D.

INHIBITION OF KERATIN FORMATION WITH UNSATURATED COMPOUNDS. P. FLESCHE. (1952) *J. invest. Derm.*, **19**, 353.

The depilatory action of locally applied vitamin A, like that of sebum, has something to do with its state of unsaturation for it is suppressed by hydrogenation. The author invites us to distinguish between the making good of a vitamin deficiency and a pharmacological side action, not only in regard to vitamin A, but also to certain other therapeutically fashionable vitamins.

J. H. T. D.

ASTEROL DIHYDROCHLORIDE IN THE TREATMENT OF DERMOPHYTOSIS CAUSED BY TRICHOPHYTON RUBRUM. J. W. WILSON, H. LEVITT and O. A. PLUNKETT. (1952) *J. invest. Derm.*, **19**, 319.

Asterol is clearly useful in the treatment of ringworm. It neither stinks nor stains, nor does it easily sensitize.

Attention, however, is drawn to evidence that immunological and other predisposing or limiting factors play an important albeit inscrutable part in recovery from ringworm.

J. H. T. D.

DEEP INFECTION OF MICE WITH TRICHOPHYTON RUBRUM. T. H. STERNBERG, J. E. TARBET, V. D. NEWCOMER and L. A. WINER. (1952) *J. invest. Derm.*, **19**, 373.

Some old cultures of *T. rubrum* were ground up and injected into the peritoneal cavities of 42 mice. There developed in 41 of them multiple granulomas, and the organisms recovered up to 25 days later grew once more on Sabouraud apparently none the worse for their experiences. After about the 35th day the mycelium began to look as if it were degenerating, and it seems

likely that the disease is self-limiting, although lesions were present up to the 85th day. And as the infection grew older new peritoneal implantation from rupture of older lesions tended to abort.

While it is not easy to make out in the microphotographs any histological resemblance to Hodgkin's disease, it is perfectly clear that not a scrap of the mycelium so well stained by McManus could be discerned in the H.E. McManus may be helpful in the diagnosis of obscure granulomas.

J. H. T. D.

SOME ENDOCRINE ASPECTS OF SKIN SENSITIZATION AND PRIMARY IRRITATION: II.

A. NILZEN. (1952) *J. invest. Derm.*, **19**, 337.

The guinea-pig is the only animal suitable for experiments with eczematoid dermatitis, and the mortality of adrenalectomy is high. Moreover it is not easy either by superficial or histological examination to distinguish between the effects of primary irritation and allergic reaction. Nevertheless the author, whose literary style must be envied by many who cannot write in their mother tongue, has succeeded in showing that the adrenals do play a part in the reaction of the skin to irritation.

J. H. T. D.

SOME OBSERVATIONS ON THE PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS.

S. C. GOLD. (1952) *J. invest. Derm.*, **19**, 333.

Serum of 3 patients with systemic L.E. was injected into the skin of rabbits without histologically demonstrable effect on the collagen. Pieces of human skin were immersed in the serum for 6-24 hours without result. It must be remembered that these pieces of skin would not have the same opportunity of absorbing the noxa of L.E. as a portion of the living skin might obtain from its normal share of the general circulation, and the pieces of skin were not necessarily derived from susceptible sites.

Anyhow, whatever the significance of this failure it does not of course exclude the possibility of an antigen-antibody reaction, which is one of the things the author would like us to believe in. The author also offers the hypothesis that the L.E. cell has its origin in a single lobe of a polymorph coming unstuck adsorbing the noxa from the plasma and thereby becoming palatable to another leucocyte, which then cannibalistically engulfs it. He makes a comparison with the "Coombs test," but without telling us what it is, or giving a reference by which the reader might find out for himself.

J. H. T. D.

FATAL SYPHILIS. G. L. M. McELLIGOTT. (1953) *Brit. J. vener. Dis.*, **29**, 58.

A very comprehensive paper, enhanced by the inclusion of four explanatory tables, which should be read in full by all practising venereologists and physicians.

W. G. A.

FATAL SYPHILIS. A REVIEW OF CERTIFICATION IN LIVERPOOL, 1938-1943. A. O. F. ROSS. (1953) *Brit. J. vener. Dis.*, **29**, 64.

Tables compiled from material obtained from a special report form of deaths from syphilis demonstrated the preponderance of male patients and institutional certifications, the relative proportions of deaths from neurosyphilis and vascular syphilis, the possibility of erroneous certification in known syphilitics and the hazards of malarial and intravenous therapy. The author also draws attention to the diminishing numbers of deaths from parenchymatous neurosyphilis and more especially from aneurysm since 1940. The tendency of untreated syphilitics to die from syphilis at an earlier age than normal and the absence of cases treated early, except in one instance, is observed.

W. G. A.

FATAL SYPHILIS. WILFRID D. NEWCOMB. (1953) *Brit. J. vener. Dis.*, **29**, 67.

The author has attempted to show the trend of syphilis in the post-mortem room at St. Mary's Hospital during the past 30 years. The incidence is remarkably small, and he wonders if in 20 years' time it will have become impossible to find the stigmata of syphilis at necropsy.

W. G. A.

SENILE SEBACEOUS ADENOMA. J. RAMOS, E. SILVA and H. PORTUGAL. (1953) *Ann. Derm. Syph.*, **80**, 121.

The authors refer to the various conditions that have been called sebaceous adenoma, and describe in detail a type occurring on the face of old people as tiny yellow tumours often with a central umbilication; they believe that these are really a hyperplasia related to the seborrhoeic state rather than true tumour.

F. F. H.